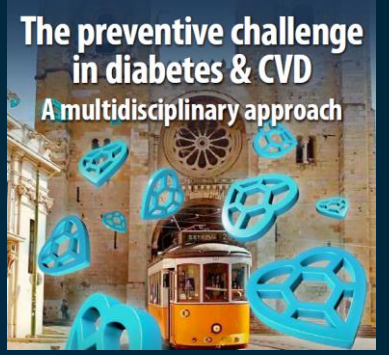


Targeting CVD in diabetes: novel strategies to tackle the risk

John Deanfield, MD
University College London
United Kingdom

PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

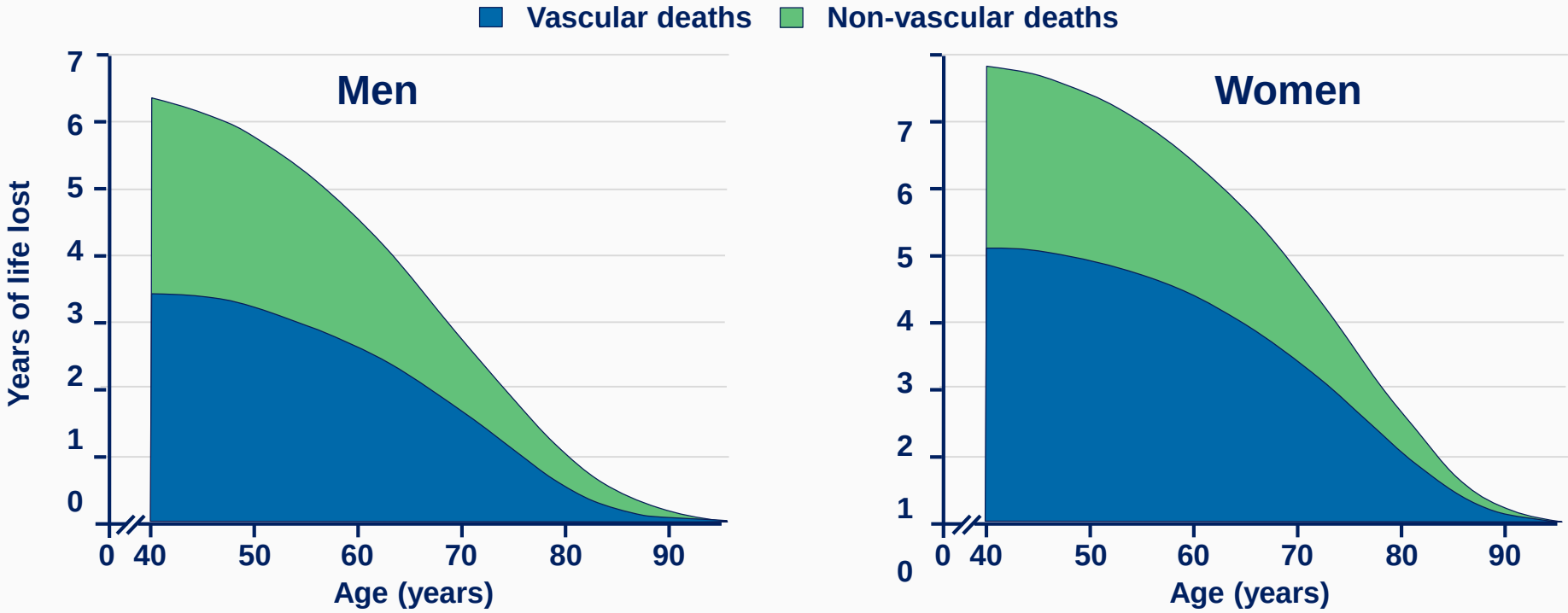
EPCOS

EBAC accredited satellite symposium held during EuroPrevent
April 11, 2019 - Lisbon, Portugal

Healthy Ageing?

CV Disease is the Major Cause of Morbidity and Mortality

CVD Challenge in Diabetes is Clear



On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes

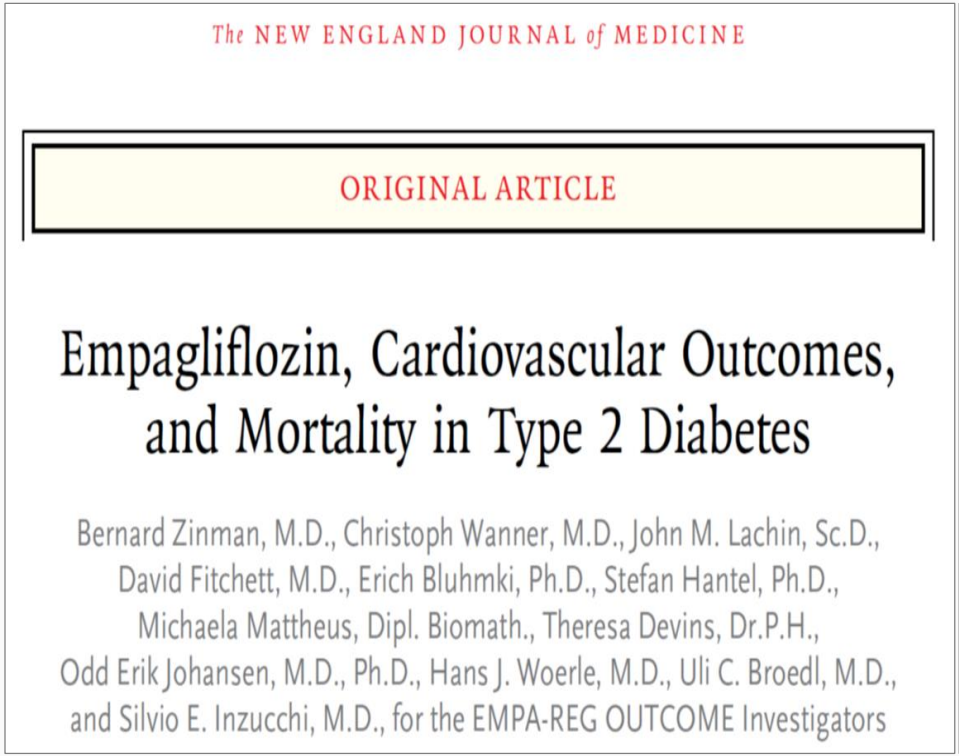
Source: Seshasai et al, N Engl J Med 2011; 364:829-41

Treatment Goals in T2DM

Management should be targeted at reducing / delaying CV complications in patients with T2DM with and without clinical CVD

Not just icing on the cake!!!

Diabetes: New Era in CVD Prevention



The NEW ENGLAND JOURNAL of MEDICINE

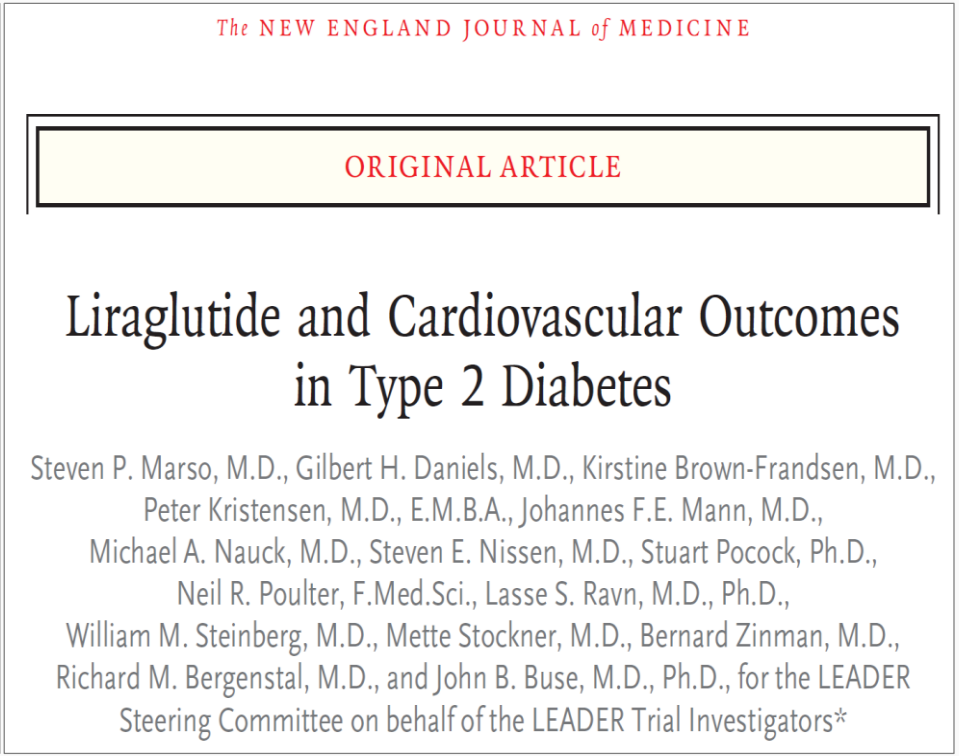
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

7,020 patients with T2DM and CV disease/risk factors 3yrs F/U

2015



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

9,340 patients with T2DM at high CV risk Median 3.8 yrs F/U

2016

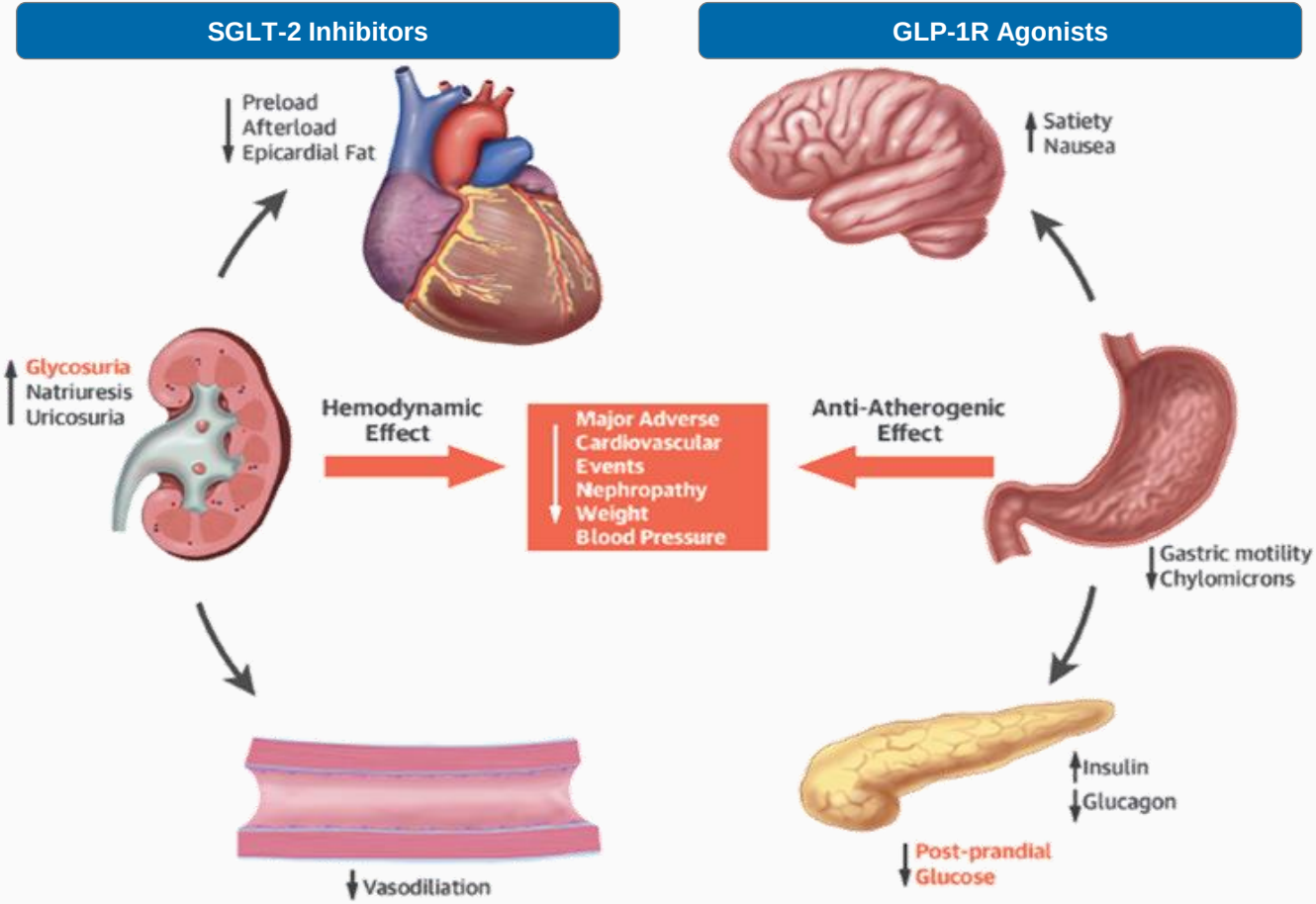
Evidence Based CV Risk Reduction

- Statins
- BP Lowering
- Metformin

GLP1-RA

SGLT2-i

Diabetes Treatment for CVD Reduction



Source: Newman JD, et al, J Am Coll Cardiol 2018; 72(15):1856-69

ADA and EASD consensus guideline

ASCVD predominates

GLP-1 RA with proven CVD benefits[1]

OR

SGLT2-i with proven CVD benefit if eGFR adequate[1-2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2-i, choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit
- DDP-IVi if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

Heart failure (HF) predominates

SGLT2-i with evidence of reducing HF in CVOT trials if eGFR adequate[2-3]

OR

GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

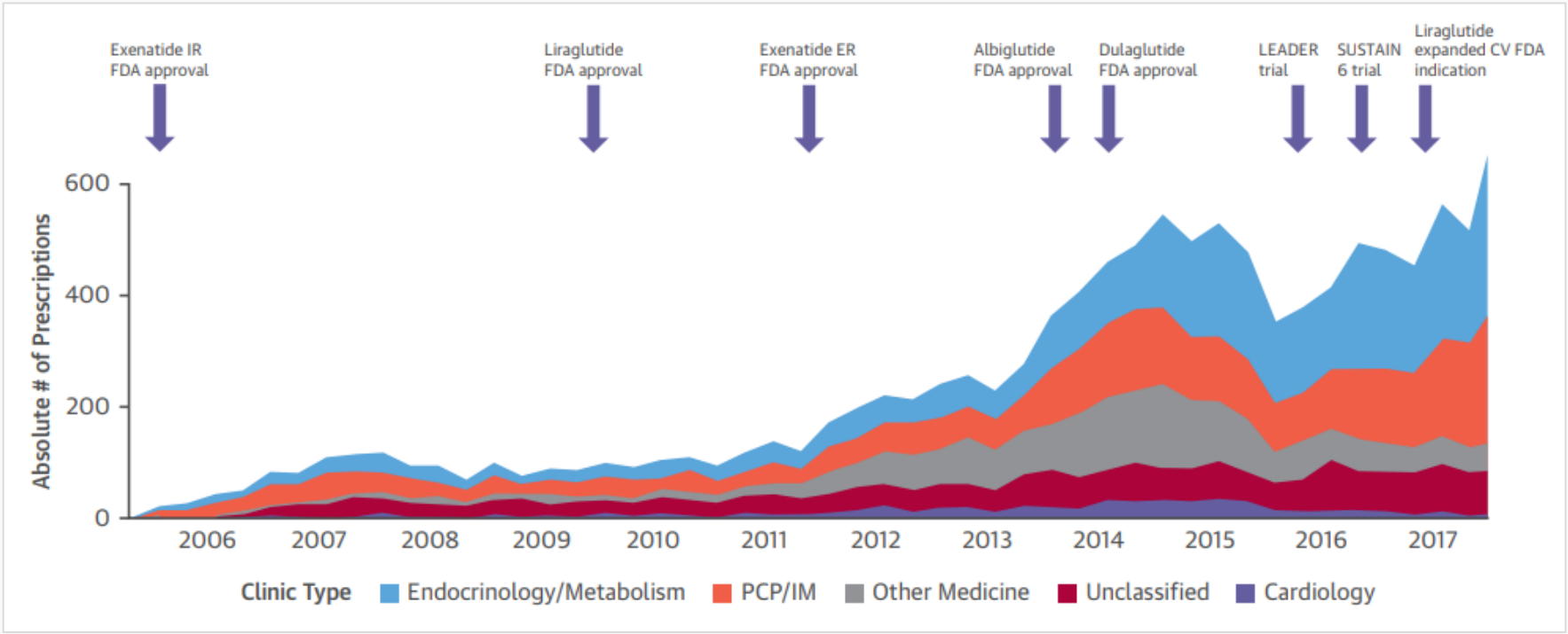
- Avoid TZD

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DDP-IVi (not Saxagliptin) if not on GLP-1 RA
- Basal insulin[4]
- SU[6]

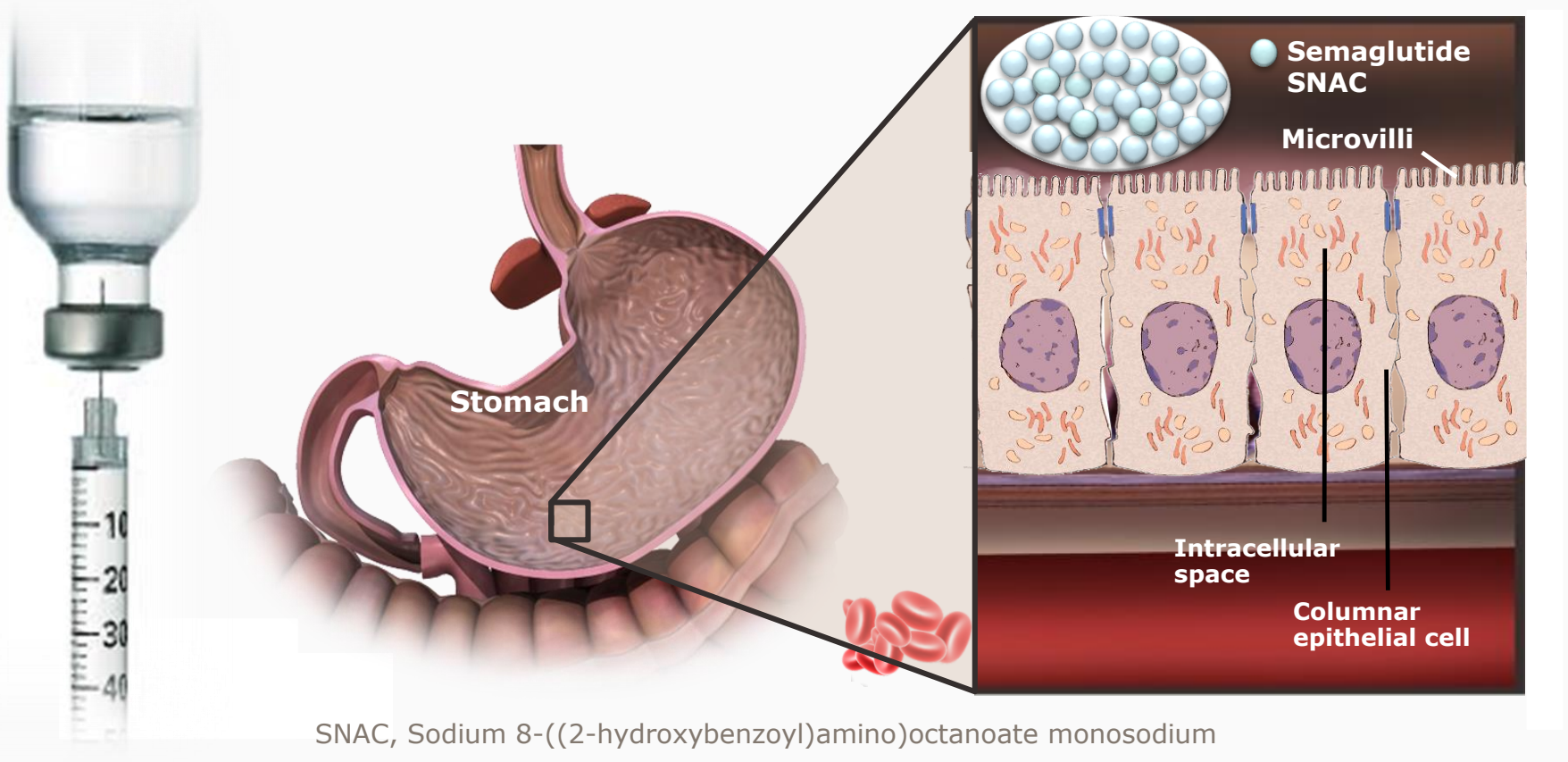
GLP1-RA Prescriptions: Partners Health Care System

7,609 patients aged 61yrs (54% women, 34% CVD)



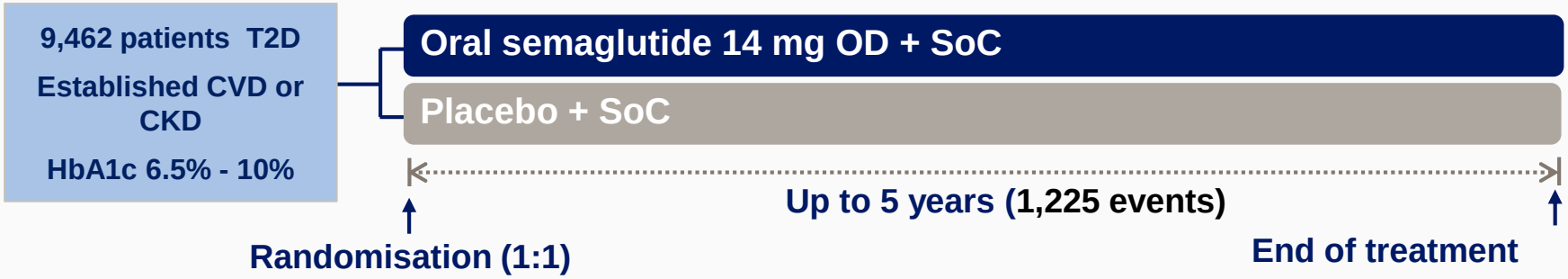
Source: Vaduganathan,M et al., JACC, 73(12) April 2019:1596-600

New Oral Formulation of SNAC and Semaglutide



SNAC, Sodium 8-((2-hydroxybenzoyl)amino)octanoate monosodium

SOUL – Trial Design

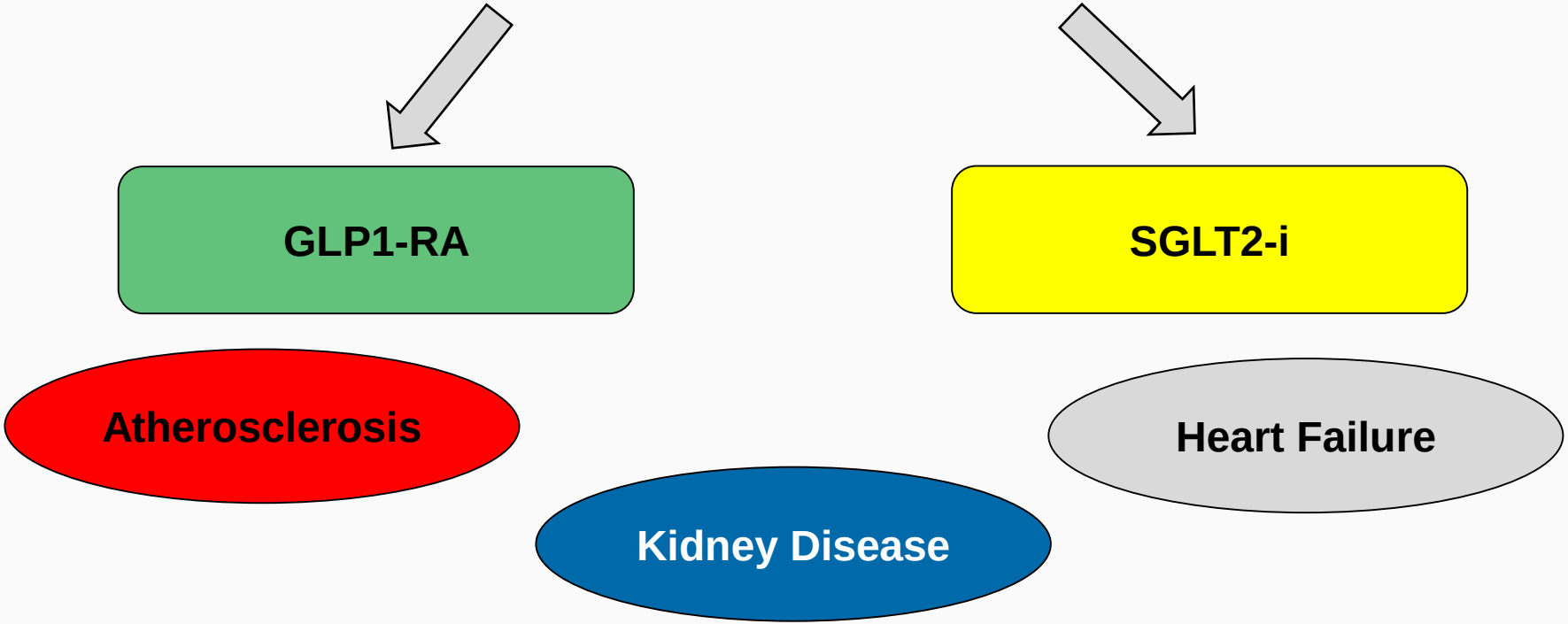


Trial objective: Demonstrate oral semaglutide lowers risk of MACE compared to placebo

Key endpoints

- **Primary: CV death, non-fatal MI or non-fatal stroke (MACE)**
- **Secondary confirmatory: 5-component composite CKD endpoint: CV death, renal death, onset of macroalbuminuria, 50% reduction in eGFR, onset of eGFR < 15 ml/min/1.73m^2 or initiation of chronic renal replacement therapy**
- **CV Death**
- **Composite PAD endpoint: Acute and chronic limb ischemia (MALE)**

Are These Two Classes ‘Cardiovascular’ Rather Than ‘Diabetes’ Drugs?

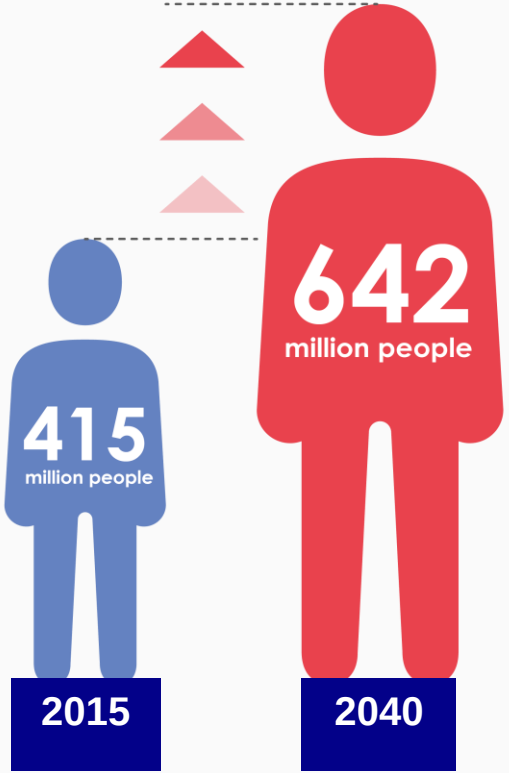


Source: Twig G et al, NEJM 2016;374:2430-40

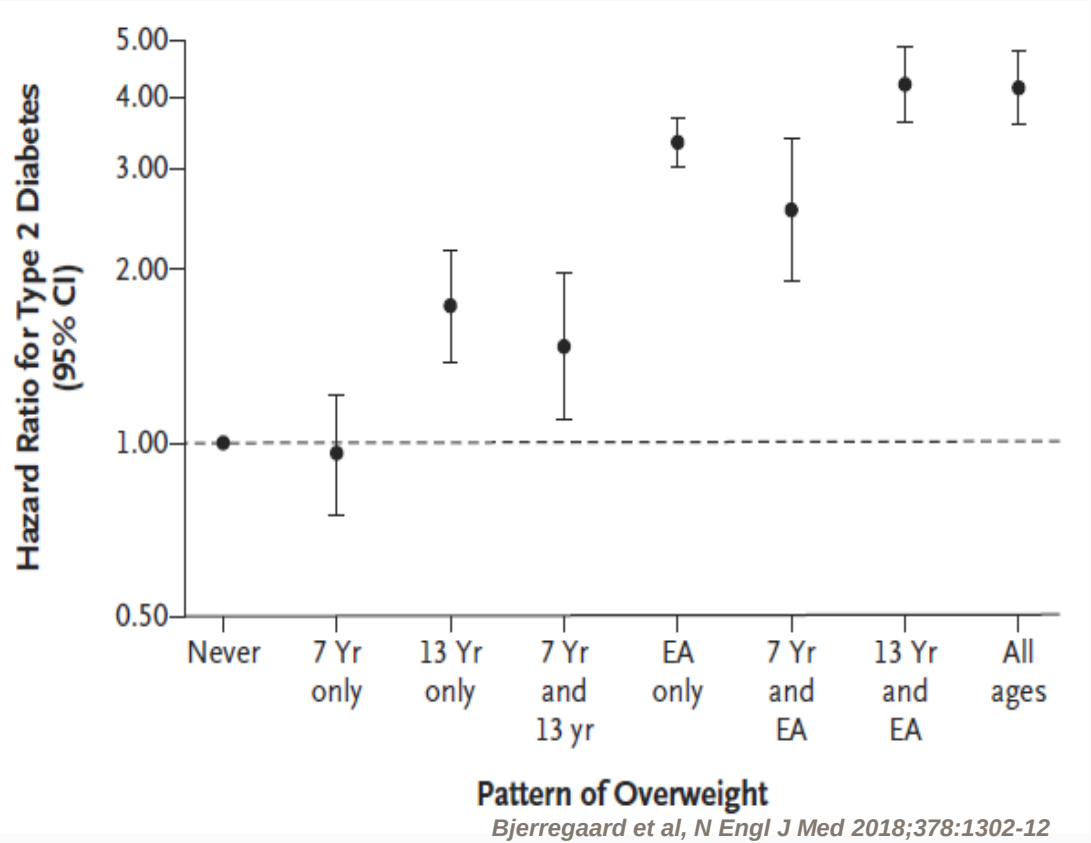
EUROPREVENT: A Thought…

"Why just strive to treat a disease like Diabetes better when you could *prevent* it?"

Diabetes Epidemic : Risk Factors start Early!



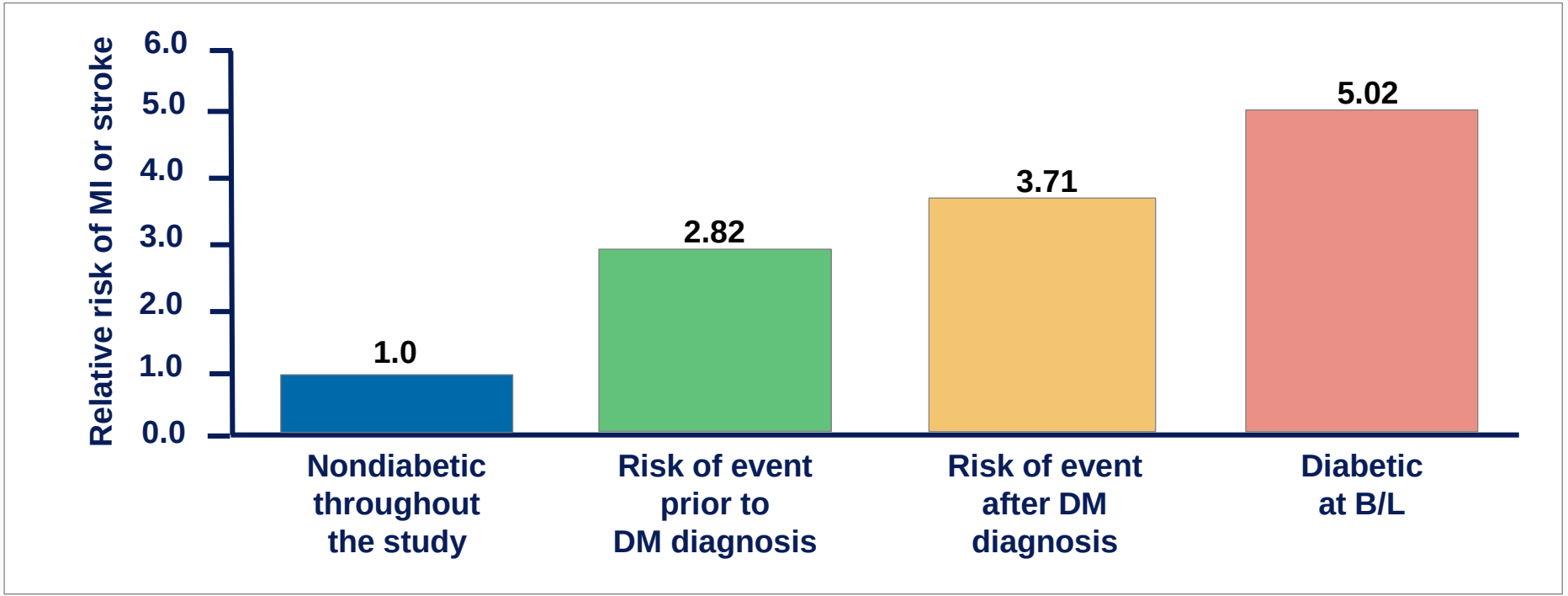
IDF Diabetes Atlas. 7th edn. 2015



Bjerregaard et al, N Engl J Med 2018;378:1302-12

The Ticking Clock: ↑ CV Risk Before ↑ Glucose (Nurses' Health Study)

20 yr F/U of 117,629 women: n=1,508 diabetes at B/L; n=5,894 developed diabetes; n=110,227 free from diabetes



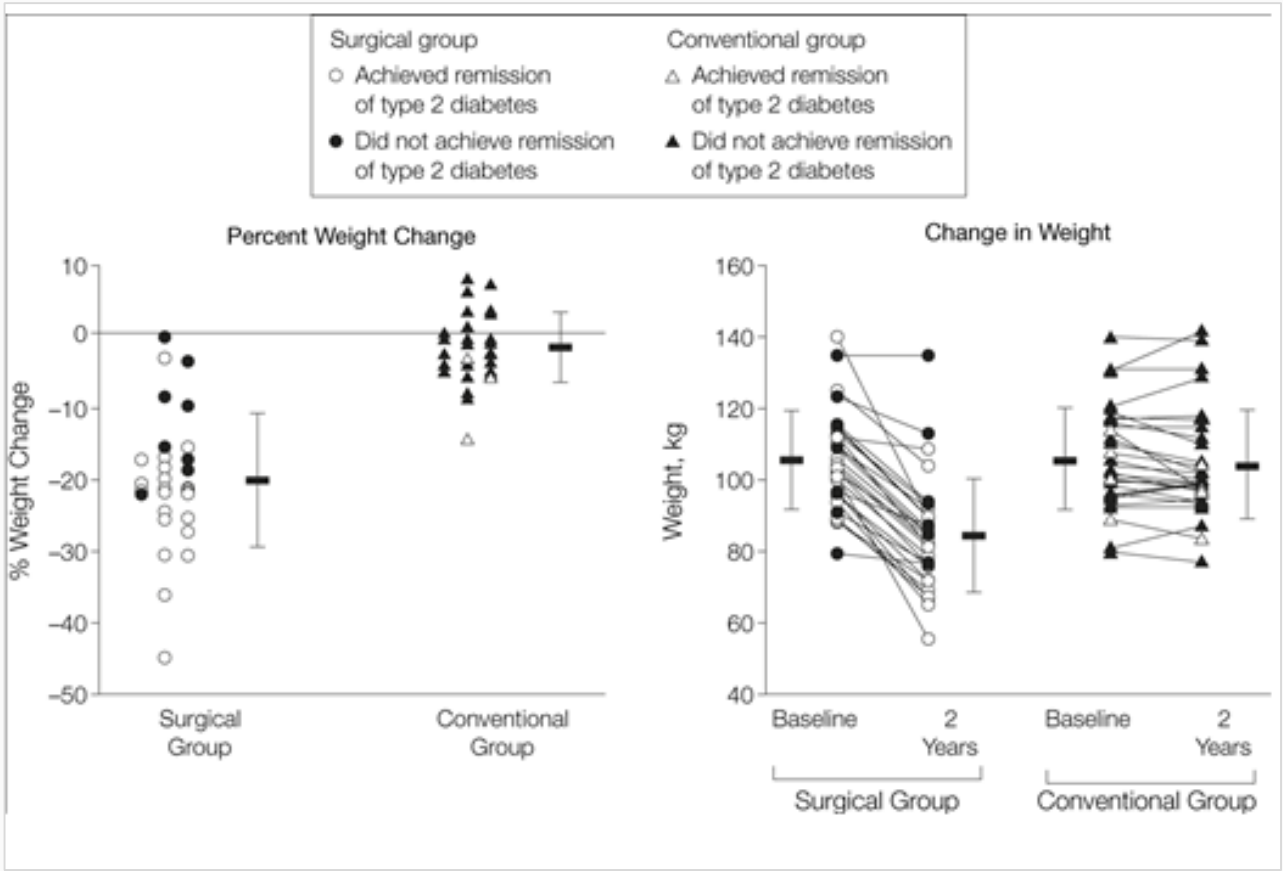
Source: Hu et al, Diabetes Care 2002; 25: 1129-1134

Obesity Exposure is KEY!

“The commonest Instruments of suicide are a knife and fork”

Martin Fischer

Weight Loss and Remission of Diabetes at 2 Yrs



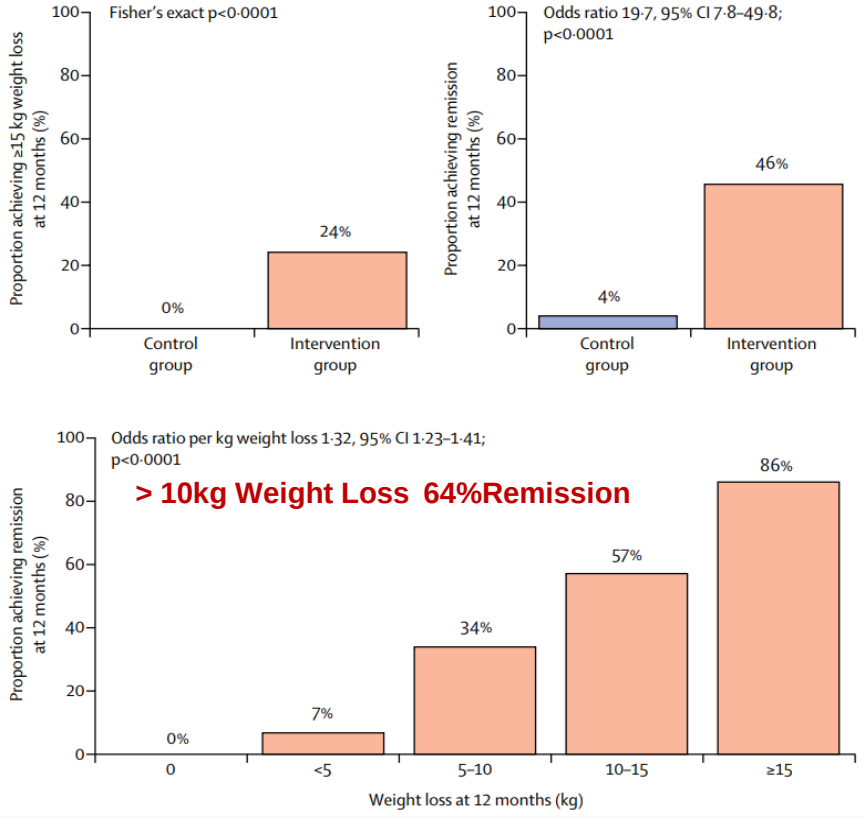
Source: Dixon, J et al, JAMA. 2008;299(3):316-323

Primary Care-led Weight Management For Remission of T2DM (DiRECT)

149 participants per group

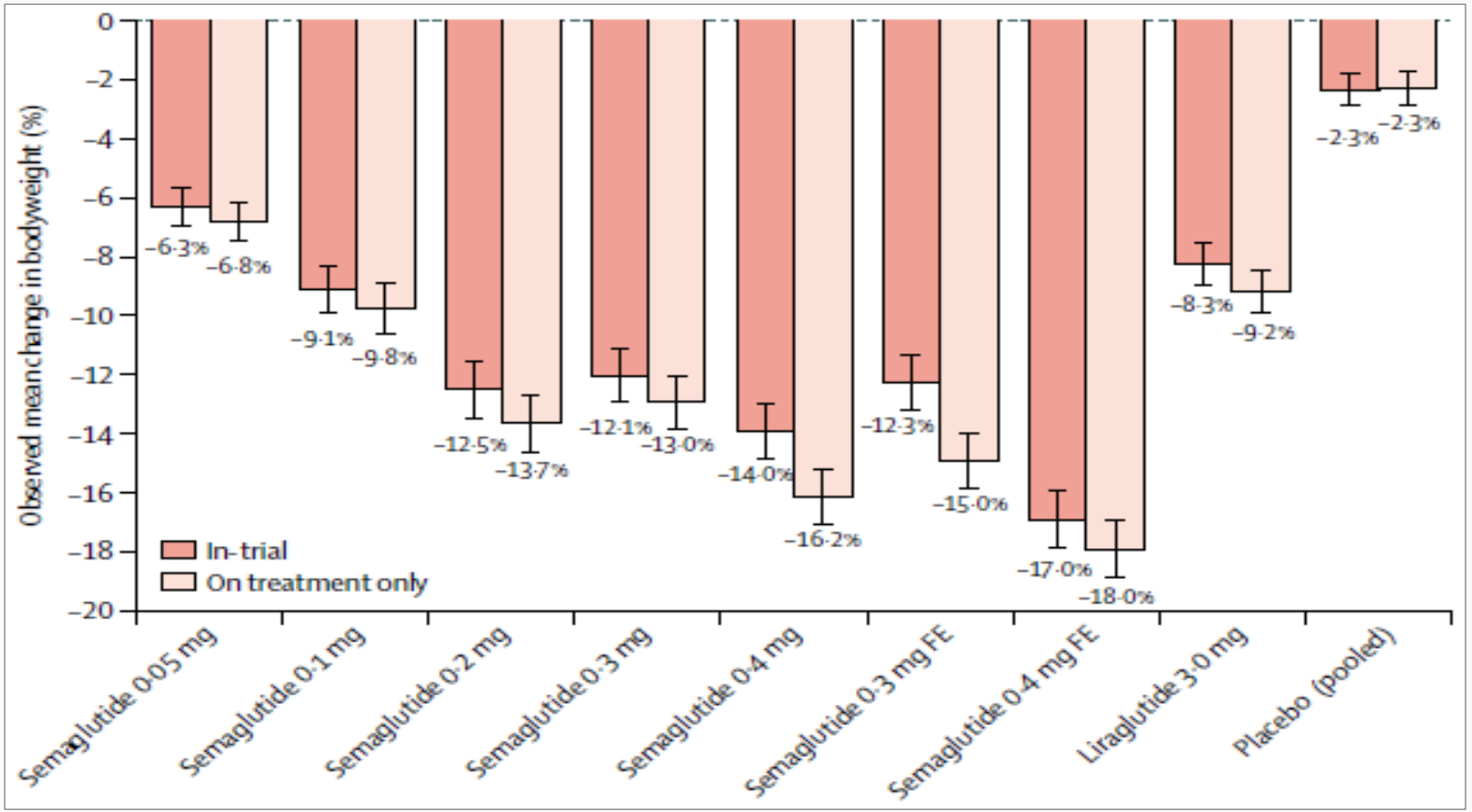
Three phases:

1. **Total Diet Replacement (12-20 weeks)**
2. **Food Reintroduction (2-8 weeks)**
3. **Weight loss Maintenance (up to 52 weeks)**



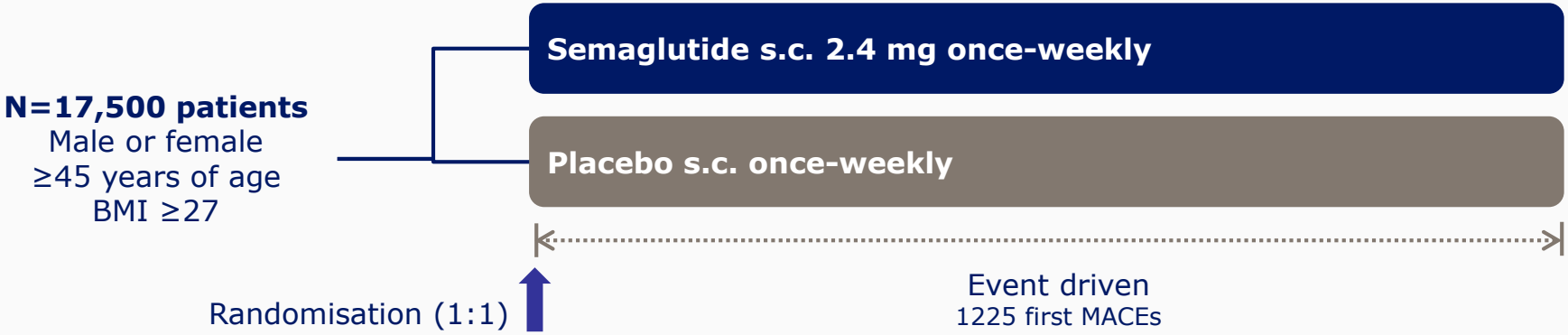
Source: Lean, M et al, Lancet 2018; 391: 541–51

Impact of GLP1-RA on Obesity



Source: O'Neil et al, Lancet 2018; 392: 637–49

SELECT: GLP1-RA in high CVD risk Non Diabetics



Prior MI	Prior stroke	PAD

Primary endpoint:
Time from randomisation to first occurrence of a composite endpoint consisting of either:

- CV death
- Non-fatal myocardial infarction
- Non-fatal stroke

Exciting New Era for CVD Management in DM

- Opportunity to improve outcomes in millions of patients with diabetes
- Likely to be benefits beyond current evidence from trials even in Non Diabetics
- Transform clinical care including the preclinical phase of cardiometabolic risk